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CHEMOTHERAPY IN SUBACUTE BACTERIAL ENDOCARDITIS

Before attempting to discuss the problem of chemotherapy in subacute bacterial endocarditis or endocarditis lenta, certain items of rather fundamental significance should be mentioned. The disease is due to the engraftment upon a previously damaged endocardium of an infection by the Streptococcus viridans. Occasionally other organisms may be responsible but these unusual types will be excluded from the present discussion. The clinical features of the disease are too well known to require repetition. Yet, because accuracy of diagnosis is essential to the correct interpretation of the results of treatment, certain criteria must be established to make reasonably sure that diagnosis is correct. These essential requirements include: 1. Clear cut evidence of organic valvular disease or of a congenital anomaly. 2. Clinical phenomena of infection, — fever, leukocytosis, increased sedimentation rate. 3. Embolic manifestations. 4. The repeated isolation of Streptococcus viridans by blood culture.

It is particularly important that there be more than a single positive blood culture as the Streptococcus viridans is known to be an accidental and transient invader of the blood stream in the absence of endocarditis lenta. Such an accidental invasion occurring in a person with pre-existing heart disease may well be confused with subacute bacterial endocarditis unless there be repeated positive blood cultures, along with one or more of the aforementioned criteria. The organism is found not infrequently in the blood during rheumatic activity, in the course of respiratory infections, following dental extractions and under a variety of other circumstances. The results of treatment will, therefore, be considered only in those cases in which diagnosis appears to have been established beyond reasonable doubt.

Spontaneous variations in virulence are known to occur with many organisms. This may well be true of the Streptococcus viridans, as suggested by Capps, who recorded four apparent cures in the years 1923 and 1924 from the use of sodium cacodylate but who has seen no recovery from its use subsequent to 1925. The phenomenal group of 23 recoveries reported by Oille and his associates (1915-1924) may possibly be explained on the same hypothesis. Furthermore, there may well be variations in the susceptibility to the chemotherapeutic agent shown by different strains of the organisms. Or, a strain initially susceptible may become resistant upon exposure to the drug in concentrations too small to inhibit its growth or cause its destruction. Both of these latter phenomena have actually been demonstrated to occur with the Streptococcus viridans.

Subacute bacterial endocarditis is subject to spontaneous remissions for weeks or even months which may simulate cure. It is, therefore, necessary that observations be extended over a sufficiently long period of time to exclude this occurrence and to make reasonably sure that there has actually been cure of the disease. Alleged cures for as short as six months time must, therefore, be rejected. Patients have been known to survive for longer than a year with only symptomatic treatment. Spontaneous recovery has been observed, though very infrequently. Libman is the only one who has recorded as high as 3 per cent of such spontaneous recoveries and the majority of students of the disease have never seen a single one. Such spontaneous recovery might coincide with some form of treatment and the result be wrongly attributed thereto. This, however, seems rather unlikely. It is well known that pronounced evidences of healing are seen frequently in the older lesions in this disease, although Streptococcus viridans may be grown from the deeper portions of such lesions. To be effective any chemotherapeutic agent, at least theoretically, should possess certain characteristics. It should be present in active form and in considerable concentration in the blood plasma. Its toxicity to the streptococcus should be greater than that to the host or to his tissues. The drug should not leave the blood stream too rapidly. Its antibacterial properties should not be neutralized by the blood or tissues of the host and, finally, it should be able to penetrate the fibrin and blood clot which surround the foci of living, multiplying organisms in concentrations adequate at least to be inhibitory.

Bearing these postulates in mind, it is not hard to understand the many recorded failures of past attempts to cure subacute bacterial endocarditis by chemotherapeutic means. The advent of the sulfonamides altered the situation in several ways and gave rise to renewed hope. Compared with compounds containing mercury or arsenic which have been used and found wanting, the sulfonamides are relatively harmless to man or can be rendered so by alkalinization and dilution. They are highly bacteriostatic for the Streptococcus viridans in concentrations in the blood which can be secured readily and be well maintained. They are known to be powerfully inhibitory to the growth of all streptococci. It is well known that in subacute bacterial endocarditis the bactericidal titre of the blood is usually high and is not impaired by the sulfonamides. Therefore, with satisfactory bacteriostasis destruction of the organisms by nature's own processes might be anticipated. Most, if not all, of the absorbable sulfonamides have been used in the attempted treatment of subacute bacterial endocartitis. While reports in the literature of treated cases are numerous, it is not feasible either to state the total number or to review all of these reports. Smith, Sauls and Stone[1] collected from the literature a total of 634 cases of the disease, six of which had recovered either without known specific treatment or spontaneously, making the recovery rate 1 per cent. On chemotherapy with sulfonamide alone recovery was noted in 6 per cent, or 12 of 198 cases. On sulfonamides plus heparin, recoveries occurred in 11.5 per cent, or 5 out of 43 cases. Combining sulfonamides with physical hyperthermia there were 16 per cent of recoveries, or 4 out of 25 cases and chemotherapy with hyperthermia produced by the intravenous injection of typhoid vaccine gave 20 per cent of recoveries, or 4 out of 21 cases.

An even more recent review of cases of subacute bacterial endocarditis has been published by Lichtman[2]. In this paper the author has included only such cases as he considers to have been adequately

treated. It is unfortunate for our present purpose that he has included in his figures cases due to Hemophilus influenzae as well as Streptococcus viridans. Nevertheless the data are highly instructive, especially as the numbers of cases in each group are larger than in any series previously presented. They are as follows:

Spontaneous recovery was noted in 1 per cent of a total of 2596 cases. This is the same rate as recorded by Smith *et al.* Under treatment with sulfonamides alone 21 of 489 patients recovered, — a rate of 4 per cent. Of this group 16 of the recoveries occurred in patients infected with the Streptococcus viridans. This is a somewhat lower rate of cure than in Smith's series. When heparin was given in conjunction with sulfonamide there were 6.5 per cent of recoveries in a group of 109 patients. That is 7 patients recovered. The number due to Streptococcus viridans is not stated. The same per cent (6.5) of recovery followed the combination of sulfonamide with physically induced fever; or 4 out of 61 patients and three of these were streptococcal. In both of these groups the recovery rates were well under those in Smith's corresponding groups. Finally sulfulnamide therapy combined with the intravenous administration of typhoid vaccine cured 7 patients, all streptococcal, out of a total of 45 treated. This is 15.5 per cent of recoveries and once more is smaller than Smith's figure.

Chemotherapy alone or combined seems definitely to have raised the recovery rate significantly above that observed to occur spontaneously. The combination of sulfonamides with heparin was intended to prevent or reduce the continued deposition of fibrin and red cells on the endocardium and thus make it possible for the sulfonamide to reach the streptococci. This procedure was suggested independently by White and Kelson and by Friedman, Hamburger and Katz. But the use of heparin appears materially to have increased the risks from cerebral and other hemorrhages due to the great prolongation of clotting time and not significantly to have increased the proportion of cures so that heparin has been, for the most part, omitted from further studies as being too dangerous.

The observation that very moderate elevation of temperature increased the bacteriostatic action of the sulfonamides lead several observers to try the combination of sulfonamide with artificially induced fever, either by means of physical methods or the intravenous injection of vaccine. Among the relatively small group of patients so treated there is, on the basis of reports in the literature, some suggestion of a rather higher rate of cure than was obtained by the combined use of sulfonamide and heparin. Even taking the best of the reported series, however, the vast majority of patients have succumbed to the disease, as has always been the case. Several observers have noted in patients dying with high blood levels of the sulfonamides that the vegetations were swarming with viable organisms.

Unrecognized variations in the virulence of the many strains of streptocci involved in the large series may explain the different degrees of success. This seems more than likely both because of the wide geographical distribution of the patients and because the studies were made by different observers over extended periods of time. It might be possible to secure a truer measure of the value of any one form of therapy by its administration to every alternate patient in a large consecutive series, as has been done in the solution of other similar problems. Desirable as this would be, it is hardly feasible because of the comparatively small number of cases of subacute bacterial endocarditis.

It must be admitted that the use of the sulfonamides combined with the administration of heparin or the induction of artificial fever has probably saved a number of lives and constitutes the first real advance in our attack upon this well nigh uniformly fatal infection. Still the chemotherapy of subacute bacterial endocarditis remains clearly rather disappointing.

In order further to improve results it is well to look for possible sources of failure in our existing methods. Probably the most frequent is due to acquired resistance of the organism to the drug from the improper and inadequate administration of sulfonamides. This is correctible if the profession will refrain from the use of any sulfonamide in any dose until diagnosis has been established and arrangements have been completed for the rapid administration of enough of the drug to raise its level in the blood to at least 5 mgm. or more per 100 cc. The value of the particular type of sulfonamide has not yet been established but inasmuch as all of them are highly bacteriostatic against the Streptococcus viridans there would seem to be little choice except on the basis of other features such as the ability of the patient to tolerate them without untoward symptoms. Sulfapyridine and sulfadiazine appear to be in greatest favor with sulfathiazole following close behind. The largest wealth of experience has been with sulfapyridine. Results might well be improved by preliminary tests made in each individual patient to determine the degree of susceptibility to the drug of his infecting strain of organisms. This has been suggested but has not yet been carried out in any large series of cases. It has been shown experimentally that although the sulfonamides may be present in high concentration, they do not penetrate the surrounding fibrin and blood clot which, therefore, mechanically isolate the nidus of living organisms. Perhaps some new derivative may yet be developed with greater powers of penetration. Until this is accomplished we will do well to continue the use of one of the current sulfonamides, probably in conjunction with some form of induced fever.

It is as yet premature to discuss the possible role which penicillin may play in treatment of this disease. It is a potent antibacterial agent with exceptionally low toxicity for man. It is but natural that it should have been tried in the treatment of bacterial endocarditis, despite the scant supply available. There is in the British Medical Journal for August 28, 1943, the report of one case treated unsuccessfully by the Floreys. The suggestion is made that enormous doses may be needed. Keefer[3] summarizes the attempts made so far under the guidance of the Research Committee of the National Research Council. Seventeen patients have received the drug in total amounts up to as high as 1,760,000 units in 26 days. Three of these showed temporary benefit but none recovered. The committee says: "There is good evidence that some strains of organisms are slightly more susceptible to penicillin than others, and there is also evidence that the blood stream can be sterilized temporarily, at least in some cases. On the whole, however, the results in the few cases treated were disappointing."

In conclusion it seems that in subacute bacterial endocarditis due to infection by Streptococcus viridans the mortality without specific treatment is about 99 per cent. That to date by chemotherapy, using the sulfonamides in combination with typhoid vaccine or physically induced fever, recovery may be expected in from 6 to 15 per cent of cases, thus reducing the expected mortality to between 94 and 85 per cent. Failure to obtain a higher measure of success seems to be largely inherent in the disease itself and to a lesser degree in such potentially controllable factors as the determination of the susceptibility of the infecting strain of organism and the avoidance of the artificial production of acquired resistance to the chemotherapeutic agent. The value of penicillin is yet to be determined.

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